THE SEARCH FOR PEOPLE WHO NEVER GET COVID

Researchers want to find people who are resistant to SARS-CoV-2, in the hope of developing new treatments.

By Smriti Mallapaty

Imagine being born naturally resistant to SARS-CoV-2, and never having to worry about contracting COVID-19 or spreading the virus. If you have this superpower, researchers want to meet you, to enrol you in their study.

As described in a paper in *Nature Immunology* last month, an international team of scientists has launched a global hunt for people who are genetically resistant to infection with the pandemic virus (E. Andreakos *et al*. *Nature Immunol*. https://doi.org/g4sh; 2021). The team hopes that identifying the genes protecting these individuals could lead to the development of virus-blocking drugs that not only protect people from COVID-19, but also prevent them from passing on the infection.

"It's a terrific idea," says Mary Carrington, an immunogeneticist at the Frederick National Laboratory for Cancer Research in Bethesda, Maryland. "Really, a wise thing to do."

But success isn't guaranteed. If genetic resistance to the coronavirus SARS-CoV-2 exists, there may be "only a handful" of people with this trait, says Isabelle Meyts, a paediatric immunologist and physician at the Catholic University of Leuven in Belgium, who is part of the consortium behind the effort.

"The question is how to find those people," says Sunil Ahuja, an infectious-diseases specialist at the University of Texas Health Science Center at San Antonio. "It's very challenging. This is not for the faint of heart."

Discordant couples

Nevertheless, the study authors, including Evangelos Andreakos, an immunologist at the Biomedical Research Foundation of the Academy of Athens, say they are confident of tracking down their quarry. "Even if we identify one, it will be really major," he says.

The first step is to narrow the search to people who have been exposed, without protection, to a sick person over an extended period, and have not tested positive or mounted an immune response against the virus. Of particular interest are people who shared a home and bed with an infected partner — pairs known as discordant couples.

The team of co-authors at 10 research centres across the world, from Brazil to Greece, have already recruited some 500 candidates, who might fit these criteria. And since the publication of their paper, at least 600 people, including some from Russia and India, have contacted them, nominating themselves as possible candidates.

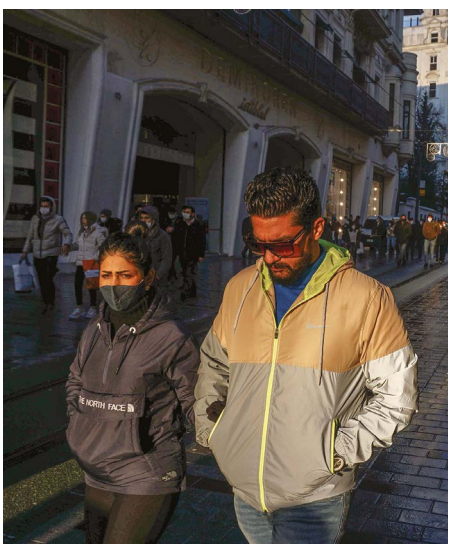
The response was a real surprise, says Jean-Laurent Casanova, a geneticist at the Rockefeller University in New York City and a co-author of the study. "I did not think for one second that people themselves, exposed and apparently not infected, would contact us."

The goal is to have at least 1,000 recruits; Andreakos says the team has already started analysing data.

A huge challenge ahead

But the researchers might have an almost impossible task, given the difficulties of proving that candidates were highly exposed to the virus, argues Ahuja. They will have to confirm that the sick partner was shedding high doses of live virus when the couple was interacting closely.

Discordant couples are not uncommon, but it is rare to find those that meet these criteria and have been regularly tested, he says. The fact that many people have now been vaccinated, potentially masking any genetic resistance to the virus, further limits the pool of people to study, Ahuja adds.



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Couples are key to the hunt for COVID resistance.

Once they have identified possible candidates, the researchers will compare the individuals' genomes with those of people who have been infected, in search of genes associated with resistance. Any contender genes will be studied in cell and animal models to confirm a causal link to resistance and establish the mechanism of action.

Casanova's team has previously identified rare mutations that make people more susceptible to severe COVID-19, but the researchers are now shifting gears to look at resistance.

In genetic surveys called genome-wide association studies (GWAS), other groups have scoured the DNA of tens of thousands of people in search of single-nucleotide changes — which typically have only a weak biological effect — and identified some possible candidate mutations associated with reduced susceptibility to infection.

One of these is found in the gene responsible for the type O blood group, but its protective effect is small, says Carrington, and it's not clear how it is conferred.

Mechanisms of resistance

The researchers behind the latest project have hypothesized the kind of resistance mechanisms they might find. The most obvious could be that some people don't have a functioning ACE2 receptor, which SARS-CoV-2 uses to enter cells. In one GWAS, posted as a preprint and therefore not peer reviewed, researchers identified a possible link between a rare mutation that probably reduces expression of the ACE2 gene and a diminished risk of infection (J. E. Horowitz *et al*. Preprint at medRxiv https://doi.org/ghqgn5; 2021).

This type of mechanism has previously been observed with HIV, the virus behind AIDS. Beginning in the 1990s, Ahuja and Carrington were involved in work that helped to identify a rare mutation that disables the CCR5 receptor on white blood cells, preventing HIV from entering them.

"That knowledge has been really useful," says Carrington. It led to a class of HIV-blocking drugs; two people were also apparently cleared of HIV after receiving bone-marrow transplants from donors with two copies of the resistant genes.

Other people resistant to SARS-CoV-2 might have very powerful immune responses, especially in the cells lining the insides of their nose. Andreakos says some people might have mutations that ramp up genes that stop the virus replicating and repackaging into new viral particles, or that break down viral RNA in the cell.

Despite the challenges ahead, he is optimistic about discovering people who are naturally resistant. "We are confident that we will find them," he says.